

# Serum Uric Acid and Risk for Cardiovascular Disease and Death: The Framingham Heart Study

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**Background:** Hyperuricemia is associated with risk for cardiovascular disease and death. However, the role of uric acid independent of established risk factors is uncertain.

**Objective:** To examine the relation of serum uric acid level to incident coronary heart disease, death from cardiovascular disease, and death from all causes.

**Design:** Community-based, prospective observational study.

**Setting:** Framingham, Massachusetts.

**Patients:** 6763 Framingham Heart Study participants (mean age, 47 years).

**Measurements:** Serum uric acid level at baseline (1971 to 1976); event rates per 1000 person-years by sex-specific uric acid quintile.

**Results:** During 117 376 person-years of follow-up, 617 coronary heart disease events, 429 cardiovascular disease deaths, and 1460 deaths from all causes occurred. In men, after adjustment for age, elevated serum uric acid level was not associated with increased risk for an adverse outcome. In women, after adjustment for age, uric acid level was predictive of coronary heart disease ( $P = 0.002$ ), death from cardiovascular disease ( $P = 0.009$ ), and death from all causes ( $P = 0.03$ ). After additional adjustment for cardiovascular disease risk factors, uric acid level was no longer associated with coronary heart disease, death from cardiovascular disease, or death from all causes. In a stepwise Cox model, diuretic use was identified as the covariate responsible for rendering serum uric acid a statistically nonsignificant predictor of outcomes.

**Conclusions:** These findings indicate that uric acid does not have a causal role in the development of coronary heart disease, death from cardiovascular disease, or death from all causes. Any apparent association with these outcomes is probably due to the association of uric acid level with other risk factors.

The association of serum uric acid with cardiovascular disease has been appreciated for nearly half a century (1). Several prospective studies have shown an association between baseline hyperuricemia and incident coronary heart disease, cardiovascular disease, and death (2–10). Despite the strength of these associations, uric acid has not been established as a causal risk factor for cardiovascular disease. Instead, uric acid seems inextricably linked to hypertension, dyslipidemia, and disordered glucose metabolism, which play a causal role in the pathogenesis of cardiovascular disease. As such, uric acid may be merely a marker of risk for cardiovascular disease.

Several recent reports, however, have attempted to dispel this notion (3, 9, 11–14). Using data from the First National Health and Nutrition Examination Study (NHANES I), Freedman and colleagues (3) demonstrated that each 60- $\mu\text{mol/L}$  increment in uric acid level was associated with a 48% increase in risk for incident ischemic heart disease among women. Furthermore, a growing body of laboratory and clinical evidence suggests that uric acid plays a role in platelet adhesiveness (15–17), formation of free radicals (18), and oxidative stress (19, 20).

As a result of this growing controversy, we revisited this question in the Framingham Heart Study sample. Longer and more contemporary follow-up and more outcome events allowed us to expand on a previous Framingham report (2). In this paper, we describe the relation of baseline serum uric acid level to 1) incident coronary heart disease events (death from coronary heart disease, recognized myocardial infarction, and coronary insufficiency), 2) death from cardiovascular disease, and 3) death from all causes. Because previous studies (2, 3, 7, 21) have suggested that uric acid is more strongly associated with adverse events in women than in men, we chose a priori to perform sex-specific analyses.

## Methods

### Study Sample

The selection criteria and study design of the Framingham Heart Study and the Framingham Off-

*Ann Intern Med.* 1999;131:7-13.

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**Table 1. Baseline Clinical Characteristics\***

| Characteristic                                 | Men<br>(n = 3075) | Women<br>(n = 3688) |
|--|-------------------|---------------------|
| Age, y   | 46 ± 15           | 48 ± 16             |
| Serum uric acid level, $\mu\text{mol/L}$       | 379 ± 76          | 285 ± 69            |
| Body mass index, $\text{kg/m}^2$               | 26.7 ± 3.6        | 24.8 ± 4.7          |
| Systolic blood pressure, mm Hg                 | 130 ± 17          | 126 ± 21            |
| Diastolic blood pressure, mm Hg                | 82 ± 11           | 77 ± 10             |
| Hypertension, %                                | 32.6              | 28.7                |
| Antihypertensive use, %                        | 8.0               | 11.6                |
| Diuretic use, %                                | 4.9               | 9.7                 |
| Left ventricular hypertrophy, %                | 0.7               | 0.4                 |
| Diabetes, %                                    | 3.9               | 2.5                 |
| Total serum cholesterol level, $\text{mmol/L}$ | 5.35 ± 1.02       | 5.40 ± 1.17         |
| Weekly alcohol use, oz                         | 5.5 ± 6.4         | 2.2 ± 3.1           |
| Smoker, %                                      | 45.9              | 37.8                |
| Postmenopausal, %                              | —                 | 49.4                |

\* Values with plus/minus sign are the mean ± SD.

spring Study have been described elsewhere (22, 23). Original participants of the Framingham Heart Study who took part in the 13th biennial examination (1972 to 1976) and adult participants in the first examination of the Framingham Offspring Study (1971 to 1975) were eligible for this investigation ( $n = 7940$ ). Blood samples for uric acid measurement were obtained in 7650 (96.3%) persons. Participants were excluded ( $n = 887$ ) for the following reasons: use of more than 2 g of salicylates per day ( $n = 17$ ), missing covariate or follow-up data ( $n = 117$ ), and prevalent cardiovascular disease ( $n = 753$ ). The remaining 6763 participants were followed prospectively until 1994.

### Baseline Measurements and Definitions

Medical histories and physical examinations were performed for each participant at every clinic visit. Systolic and diastolic blood pressure were measured twice in the left arm of seated participants by using a mercury-column sphygmomanometer positioned near eye level. The average of the two readings was used for each blood pressure variable. The diagnosis of hypertension was based on a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or the current use of antihypertensive drugs (24).

Height and weight were measured at each examination, and body mass index was calculated as the weight in kilograms divided by the square of the height in meters. Participants who reported smoking at least one cigarette per day during the year before the examination were classified as current smokers. Alcohol use was ascertained by self-report and was categorized as ounces of ethanol consumed per week. Menopause was defined as the absence of menses for 1 year or more.

Diabetes was defined on the basis of a nonfasting blood glucose level of 11.1 mmol/L (200 mg/dL) or greater, a fasting blood glucose level of 7.8 mmol/L

(140 mg/dL) or greater, or the use of insulin or an oral hypoglycemic agent.

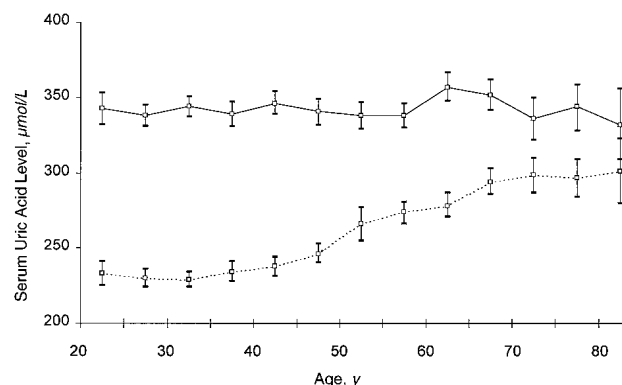
Serum uric acid levels were measured with an autoanalyzer that used a phosphotungstic acid reagent (25). Cholesterol levels were determined according to the Abell-Kendall method (26).

### Outcome Events

The primary outcome measures were incident coronary heart disease events, death from cardiovascular disease (coronary heart disease, congestive heart failure, stroke, or other cardiovascular disease), and death from all causes. Coronary heart disease events included the following: death from coronary heart disease (available information suggested coronary heart disease as the probable cause), recognized myocardial infarction (serial electrocardiographic changes leading to development of new pathologic Q waves, characteristic increase and decrease in serum myocardial markers with a suggestive clinical history, or evidence at necropsy of new or recent infarction), and coronary insufficiency (prolonged ischemic chest discomfort associated with transient repolarization abnormality, without criteria for myocardial infarction). Events that were more equivocal, such as unrecognized myocardial infarction and angina pectoris, were not included as coronary heart disease events for this analysis. A panel of three physicians determined the outcome events according to previously published criteria (27) after reviewing Framingham Heart Study and outside hospital and physician records.

### Statistical Analysis

Separate analyses were performed for men and women. All participants were divided according to sex-specific uric acid quintiles. Crude event rates were calculated for each quintile. Cox proportional hazards regression models (28) were used to examine the relations of uric acid quintiles (with quintile 1 as the reference category) and the relation of uric



**Figure.** Mean serum uric acid level by sex and 5-year age group. Solid line represents men; dashed line represents women; squares represent values at midpoint of 5-year age group; and vertical bars represent 95% CIs.

**Table 2. Relations of Serum Uric Acid Level to Coronary Heart Disease, Death from Cardiovascular Disease, and Death from All Causes**

| Uric Acid Quintile                | Events, <i>n</i> | Rate per 1000<br>Person-Years | Hazard Ratio (95% CI) |                  |                  |
|-----------------------------------|------------------|-------------------------------|-----------------------|------------------|------------------|
|                                   |                  |                               | Unadjusted            | Adjusted for Age | Fully Adjusted*  |
| Coronary heart disease            |                  |                               |                       |                  |                  |
| Men                               |                  |                               |                       |                  |                  |
| Quintile 1 (<280 μmol/L)          | 86               | 8.7                           | 1                     | 1                | 1                |
| Quintile 2 (280–315 μmol/L)       | 90               | 8.8                           | 1.01 (0.75–1.36)      | 1.08 (0.80–1.45) | 1.13 (0.84–1.53) |
| Quintile 3 (316–351 μmol/L)       | 63               | 6.1                           | 0.70 (0.51–0.97)      | 0.80 (0.57–1.10) | 0.85 (0.61–1.19) |
| Quintile 4 (352–399 μmol/L)       | 83               | 7.9                           | 0.90 (0.67–1.22)      | 0.94 (0.70–1.27) | 0.94 (0.69–1.28) |
| Quintile 5 (≥400 μmol/L)          | 72               | 7.2                           | 0.83 (0.60–1.13)      | 0.77 (0.56–1.05) | 0.73 (0.52–1.02) |
| <i>P</i> for trend                |                  |                               | 0.15                  | 0.06             | 0.03             |
| Women                             |                  |                               |                       |                  |                  |
| Quintile 1 (<196 μmol/L)          | 25               | 1.9                           | 1                     | 1                | 1                |
| Quintile 2 (196–226 μmol/L)       | 24               | 1.8                           | 0.99 (0.57–1.74)      | 0.97 (0.55–1.69) | 0.92 (0.52–1.61) |
| Quintile 3 (227–262 μmol/L)       | 36               | 2.7                           | 1.47 (0.89–2.46)      | 1.29 (0.78–2.15) | 1.18 (0.71–1.97) |
| Quintile 4 (263–310 μmol/L)       | 50               | 4.0                           | 2.17 (1.35–3.52)      | 1.20 (0.74–1.95) | 1.05 (0.64–1.71) |
| Quintile 5 (≥311 μmol/L)          | 88               | 7.5                           | 4.11 (2.64–6.42)      | 1.80 (1.15–2.84) | 1.25 (0.78–2.02) |
| <i>P</i> for trend                |                  |                               | <0.001                | 0.002            | >0.2             |
| Death from cardiovascular disease |                  |                               |                       |                  |                  |
| Men                               |                  |                               |                       |                  |                  |
| Quintile 1 (<280 μmol/L)          | 47               | 4.6                           | 1                     | 1                | 1                |
| Quintile 2 (280–315 μmol/L)       | 52               | 4.8                           | 1.07 (0.72–1.59)      | 1.18 (0.79–1.75) | 1.21 (0.80–1.81) |
| Quintile 3 (316–351 μmol/L)       | 34               | 3.2                           | 0.70 (0.45–1.09)      | 0.84 (0.54–1.31) | 0.90 (0.58–1.42) |
| Quintile 4 (352–399 μmol/L)       | 49               | 4.5                           | 0.98 (0.66–1.46)      | 1.04 (0.70–1.56) | 0.99 (0.65–1.49) |
| Quintile 5 (≥400 μmol/L)          | 50               | 4.9                           | 1.08 (0.72–1.60)      | 1.02 (0.69–1.52) | 0.92 (0.61–1.40) |
| <i>P</i> for trend                |                  |                               | >0.2                  | >0.2             | >0.2             |
| Women                             |                  |                               |                       |                  |                  |
| Quintile 1 (<196 μmol/L)          | 17               | 1.3                           | 1                     | 1                | 1                |
| Quintile 2 (196–226 μmol/L)       | 23               | 1.8                           | 1.39 (0.74–2.61)      | 1.29 (0.69–2.42) | 1.24 (0.66–2.34) |
| Quintile 3 (227–262 μmol/L)       | 28               | 2.1                           | 1.68 (0.92–3.07)      | 1.46 (0.80–2.66) | 1.38 (0.75–2.54) |
| Quintile 4 (263–310 μmol/L)       | 45               | 3.6                           | 2.85 (1.63–4.98)      | 1.37 (0.79–2.41) | 1.26 (0.72–2.22) |
| Quintile 5 (≥311 μmol/L)          | 84               | 7.0                           | 5.69 (3.38–9.58)      | 1.93 (1.14–3.26) | 1.46 (0.84–2.53) |
| <i>P</i> for trend                |                  |                               | <0.001                | 0.009            | >0.2             |
| Death from all causes             |                  |                               |                       |                  |                  |
| Men                               |                  |                               |                       |                  |                  |
| Quintile 1 (<280 μmol/L)          | 154              | 15.0                          | 1                     | 1                | 1                |
| Quintile 2 (280–315 μmol/L)       | 170              | 15.8                          | 1.07 (0.86–1.33)      | 1.17 (0.94–1.46) | 1.24 (0.99–1.54) |
| Quintile 3 (316–351 μmol/L)       | 105              | 9.9                           | 0.66 (0.51–0.85)      | 0.79 (0.61–1.01) | 0.85 (0.66–1.10) |
| Quintile 4 (352–399 μmol/L)       | 143              | 13.1                          | 0.87 (0.70–1.10)      | 0.93 (0.74–1.17) | 0.96 (0.76–1.21) |
| Quintile 5 (≥400 μmol/L)          | 157              | 15.3                          | 1.04 (0.83–1.29)      | 0.98 (0.78–1.22) | 0.98 (0.78–1.24) |
| <i>P</i> for trend                |                  |                               | >0.2                  | >0.2             | >0.2             |
| Women                             |                  |                               |                       |                  |                  |
| Quintile 1 (<196 μmol/L)          | 85               | 6.3                           | 1                     | 1                | 1                |
| Quintile 2 (196–226 μmol/L)       | 99               | 7.5                           | 1.19 (0.89–1.60)      | 1.11 (0.83–1.48) | 1.07 (0.80–1.43) |
| Quintile 3 (227–262 μmol/L)       | 111              | 8.3                           | 1.31 (0.99–1.74)      | 1.15 (0.87–1.53) | 1.11 (0.84–1.48) |
| Quintile 4 (263–310 μmol/L)       | 174              | 13.8                          | 2.22 (1.71–2.88)      | 1.13 (0.87–1.47) | 1.09 (0.84–1.42) |
| Quintile 5 (≥311 μmol/L)          | 262              | 21.8                          | 3.63 (2.84–4.63)      | 1.32 (1.03–1.70) | 1.16 (0.89–1.51) |
| <i>P</i> for trend                |                  |                               | <0.001                | 0.03             | >0.2             |

\* Adjusted for age, body mass index, systolic blood pressure, use of antihypertensive agents, use of diuretics, diabetes, total cholesterol level, smoking status, alcohol intake, left ventricular hypertrophy, and menopausal status.

acid level as a continuous variable to incidence of coronary heart disease events, cardiovascular disease mortality rates, and all-cause mortality rates. For comparative purposes, hazard ratios were calculated without adjustment. For inferential purposes, hazard ratios were calculated with adjustment for age only and also with adjustment for age and other clinical variables associated with uric acid level or atherosclerotic events: body mass index ( $\text{kg}/\text{m}^2$ ), diabetes (yes/no), systolic blood pressure (mm Hg), current diuretic use (yes/no), use of antihypertensive medications other than diuretics (yes/no), left ventricular hypertrophy shown on electrocardiography (yes/no), total cholesterol level (mmol/L), smoking status (yes/no), alcohol use (ounces consumed per week), and menopausal status in women (yes/no). Post hoc subgroup analyses were done to determine any possible relations between quintiles

of uric acid and the outcome events in participants stratified according to diuretic use and hypertension status.

All analyses were performed on a Sun Ultra-SPARC computer (Sun Microsystems, Mountain View, California) using SAS software (SAS Institute, Cary, North Carolina) (29). A two-sided *P* value less than 0.05 was the criterion for statistical significance.

## Results

### Participant Characteristics

Table 1 shows the baseline clinical characteristics for men and women. The mean uric acid level was 379  $\mu\text{mol/L}$  in men (range, 119 to 738  $\mu\text{mol/L}$ ) and 285  $\mu\text{mol/L}$  in women (range, 24 to 696  $\mu\text{mol/L}$ ).

**Table 3. P Values for Uric Acid Quintile Trend among Women in Stepwise Cox Proportional Hazards Analyses**

| Step | Coronary Heart Disease       |         | Death from Cardiovascular Disease |         | Death from All Causes        |         |
|------|------------------------------|---------|-----------------------------------|---------|------------------------------|---------|
|      | Covariate                    | P Value | Covariate                         | P Value | Covariate                    | P Value |
| 0*   |                              | 0.002   |                                   | 0.009   |                              | 0.026   |
| 1    | Systolic blood pressure      | 0.008   | Systolic blood pressure           | 0.013   | Smoking                      | 0.043   |
| 2    | Cholesterol level            | 0.031   | Diabetes                          | 0.016   | Systolic blood pressure      | 0.064   |
| 3    | Smoking                      | 0.044   | Smoking                           | 0.018   | Diabetes                     | 0.081   |
| 4    | Diabetes                     | 0.046   | Diuretic treatment                | 0.072   | Diuretic treatment           | >0.2    |
| 5    | Diuretic treatment           | 0.18    | Left ventricular hypertrophy      | 0.090   | Hypertension treatment†      | >0.2    |
| 6    | Body mass index              | 0.2     | Cholesterol level                 | 0.13    | Left ventricular hypertrophy | >0.2    |
| 7    | Left ventricular hypertrophy | >0.2    | Hypertension treatment†           | 0.17    | Cholesterol level            | >0.2    |

\* All models include age and uric acid quintile.

† Other than treatment with diuretics.

The effect of age on mean serum uric acid level is illustrated in the **Figure**. In men, uric acid levels changed minimally with age. In women, mean serum uric acid levels gradually increased from the fourth to the seventh decades of life. Furthermore, among women 30 to 54 years of age, the mean serum uric acid level was 5 to 13  $\mu\text{mol/L}$  greater in those who were postmenopausal (data not shown).

### Uric Acid Level and Outcome Events

There were 117 376 person-years of follow-up. In men, 394 coronary heart disease events, 232 deaths due to cardiovascular disease, and 729 deaths from all causes occurred. As a continuous variable, baseline uric acid level was not associated with increased risk for any end point in men. In fully adjusted Cox models, for every 60- $\mu\text{mol/L}$  increase in serum uric acid level, hazard ratios were as follows: 0.91 (95% CI, 0.83 to 0.99) for coronary heart disease, 0.95 (CI, 0.86 to 1.06) for death from cardiovascular disease, and 0.97 (CI, 0.91 to 1.03) for death from all causes. In men, baseline quintile of serum uric acid level was also not associated with increased risk for any outcome measure. Uric acid level was inversely related to coronary heart disease in the full multivariable adjusted model (**Table 2**).

In women, 223 coronary heart disease events, 197 deaths from cardiovascular disease, and 731 deaths from all causes occurred. From quintile 1 to quintile 5, crude rates increased more than threefold for coronary heart disease (from 1.9 to 7.5 per 1000 person-years), death from cardiovascular disease (from 1.3 to 7.0 per 1000 person-years) and death from all causes (from 6.3 to 21.8 per 1000 person-years) (**Table 2**). In unadjusted Cox models in which quintile 1 was the reference category, risk significantly increased with increasing uric acid quintile for all three outcome measures ( $P < 0.001$  for trend). This trend diminished after adjustment for age but remained significant for coronary heart disease ( $P = 0.002$ ), death from cardiovascular disease ( $P = 0.009$ ), and death from all causes ( $P = 0.03$ ). In fully adjusted Cox models, baseline uric acid

level was no longer associated with increased risk for coronary heart disease ( $P > 0.2$  for trend), death from cardiovascular disease ( $P = 0.23$ ), or death from all causes ( $P > 0.2$ ). Similar relations were found when baseline uric acid level was assessed as a continuous variable. In the fully adjusted models, hazard ratios for every 60- $\mu\text{mol/L}$  increase in serum uric acid level were as follows: 1.05 (CI, 0.94 to 1.17) for coronary heart disease, 1.01 (CI, 0.90 to 1.13) for death from cardiovascular disease, and 1.03 (CI, 0.97 to 1.09) for death from all causes.

To identify the covariates largely responsible for the declining association between baseline uric acid level and the outcome measures among women, we assessed the  $P$  value for quintile trend after each covariate was added to the stepwise Cox models (**Table 3**). Established risk factors, such as blood pressure, smoking, total cholesterol level, diabetes, and diuretic use were responsible for the declining quintile trend with each end point.

### Subgroup Analyses

Approximately one third of men and 30% of women were hypertensive, and 5% of men and 10% of women were receiving diuretics. Among these subgroups, baseline uric acid level was not associated with subsequent coronary heart disease, death from cardiovascular disease, or death from all causes (**Table 4**).

## Discussion

In this prospective community-based study of 6763 men and women, serum uric acid level was not associated with increased risk for coronary heart disease, death from cardiovascular disease, or death from all causes after adjustment for risk factors and potential confounders. Although our findings are negative and contrary to those recently reported (3, 6, 9, 11–13), they provide insight into the association between uric acid and cardiovascular disease. We also offer an explanation for the discrepancy

between our results and findings of other studies that had suggested a positive association between uric acid and cardiovascular outcomes.

Prospective studies examining the relation of serum uric acid level to incident cardiovascular events have differed substantially in study design. These differences probably explain the disparate results in the literature. Some authors combined the results for men and women after adjustment for sex (8, 9, 12, 13), whereas others performed sex-specific analyses (2–4, 7). We believed a priori that sex-specific analyses were required because at all ages, the serum uric acid level is higher in men than in women (Figure 1). In addition, previous studies have suggested that uric acid levels are more strongly associated with adverse events in women than in men (2, 3, 7, 21). Uric acid is also associated with diabetes and glucose intolerance, risk factors that confer greater relative risk for cardiovascular disease in women (30–32).

The management of prevalent cardiovascular disease at the inception of each of these previous studies has also varied considerably. Most studies did not exclude persons with cardiovascular disease at baseline (4, 8, 9, 12, 13) or excluded only those with prevalent coronary heart disease but not other manifestations of cardiovascular disease (2, 3, 5). With such an approach, it is inherently difficult to determine whether incident cardiovascular disease events are related to the preexisting disease or to the uric acid level. Because our goal was to determine the relation of baseline serum uric acid level to initial incident cardiovascular events, we considered it necessary to exclude participants with prevalent cardiovascular disease at baseline.

The degree of adjustment for possible confounding variables has also differed substantially among

the observational studies to date. Although most authors controlled for age, relative weight, blood pressure, and serum cholesterol level, many of the same investigators did not adjust for diabetes (2, 4), antihypertensive therapy (4–6), or diuretic use (4, 6, 7). A recent report (3) seems to have accounted for diabetes by excluding diabetic patients from the longitudinal analyses, but diabetes was identified solely by self-report. A misclassification bias may be responsible for residual confounding because about half of persons with type 2 diabetes are unaware of their diagnosis (33).

Among men in our study, elevated serum uric acid level was associated with decreased incidence of coronary heart disease. We found no association between baseline serum uric acid level and death from cardiovascular disease or death from all causes. The unexpected inverse relation between uric acid level and coronary heart disease is difficult to explain and may be the result of chance associated with the testing of multiple hypotheses. Another possibility is that the finding may reflect prolonged event-free survival of persons of high socioeconomic status, in whom hyperuricemia and gout are more common (34, 35). Unfortunately, the information necessary to adjust for socioeconomic status in the current study was unavailable.

With the exception of two investigations (6, 11), most previous prospective studies have not found a positive association between serum uric acid level and risk for cardiovascular disease in men. Differences in participant characteristics or statistical techniques may explain the discrepancy between the results in an Augsburg, Germany, cohort and our findings. Mean total cholesterol levels and mean systolic and diastolic blood pressures in the German cohort (36) were greater than those in Framingham

**Table 4. Risk for Outcome Events in the Subgroup with Hypertension and the Subgroup Receiving Diuretics\***

| Subgroup           | Participants at Risk | Coronary Heart Disease |                       | Death from Cardiovascular Disease |                       | Death from All Causes |                       |
|--------------------|----------------------|------------------------|-----------------------|-----------------------------------|-----------------------|-----------------------|-----------------------|
|                    |                      | Events                 | Hazard Ratio (95% CI) | Events                            | Hazard Ratio (95% CI) | Events                | Hazard Ratio (95% CI) |
|                    | <i>n</i>             |                        |                       | <i>n</i>                          |                       | <i>n</i>              |                       |
| Hypertension       |                      |                        |                       |                                   |                       |                       |                       |
| Men                |                      |                        |                       |                                   |                       |                       |                       |
| No                 | 2074                 | 210                    | 0.90 (0.81–1.00)      | 105                               | 1.05 (0.91–1.21)      | 369                   | 0.95 (0.88–1.02)      |
| Yes                | 1001                 | 184                    | 0.94 (0.85–1.05)      | 127                               | 0.92 (0.81–1.04)      | 360                   | 0.99 (0.92–1.07)      |
| Women              |                      |                        |                       |                                   |                       |                       |                       |
| No                 | 2627                 | 81                     | 1.05 (0.88–1.24)      | 57                                | 1.00 (0.82–1.23)      | 305                   | 1.06 (0.97–1.15)      |
| Yes                | 1060                 | 142                    | 1.07 (0.93–1.22)      | 140                               | 1.10 (0.96–1.27)      | 426                   | 1.02 (0.95–1.10)      |
| Diuretic treatment |                      |                        |                       |                                   |                       |                       |                       |
| Men                |                      |                        |                       |                                   |                       |                       |                       |
| No                 | 2923                 | 361                    | 0.92 (0.79–1.07)      | 209                               | 0.95 (0.86–1.04)      | 659                   | 0.97 (0.92–1.09)      |
| Yes                | 152                  | 33                     | 0.87 (0.76–1.12)      | 23                                | 1.07 (0.78–1.48)      | 70                    | 0.94 (0.79–1.13)      |
| Women              |                      |                        |                       |                                   |                       |                       |                       |
| No                 | 3329                 | 162                    | 1.00 (0.88–1.12)      | 140                               | 1.04 (0.92–1.18)      | 569                   | 1.02 (0.96–1.09)      |
| Yes                | 358                  | 61                     | 1.27 (0.97–1.66)      | 57                                | 1.17 (0.90–1.52)      | 162                   | 1.03 (0.89–1.19)      |

\* Hazard ratios are given for uric acid quintile trend. Analyses adjusted for age, body mass index, systolic blood pressure, use of antihypertensive agents (in the diuretic subgroup), use of diuretics (in the hypertension subgroup), diabetes, total cholesterol level, smoking status, alcohol intake, left ventricular hypertrophy, and menopausal status (among women).

men of similar age. Furthermore, the German study did not adjust for three relevant confounders: altered glucose metabolism, relative weight, and diuretic use. In the Honolulu Heart Study (6), elevated uric acid level was associated with incident angina in men. Again, the investigators did not adjust for diuretic use. In addition, when the coronary heart disease outcome was analyzed by using definite coronary heart disease instead of the more equivocal outcome, uric acid level was no longer associated with coronary events.

Among women, we found a strong and graded association between baseline uric acid level and increased risk for coronary heart disease, death from cardiovascular disease, and death from all causes. These findings are similar to those seen in previous studies (2–5, 7). This risk was reduced substantially after adjustment for age, and it was eliminated completely in the multivariate model. In a subsequent stepwise Cox analysis, we identified the covariates responsible for the loss of uric acid's statistical significance: blood pressure, total cholesterol level, smoking, diabetes, and, in particular, diuretic therapy. In addition to inducing hyperuricemia, diuretic therapy frequently worsens lipid levels and glucose tolerance (37–40). Furthermore, diuretic therapy is probably a marker for more severe hypertension.

Mechanisms by which uric acid may be associated with atherosclerotic disease remain uncertain. A large body of evidence links uric acid with the metabolic syndrome of insulin resistance, obesity, hypertension, and dyslipidemia (41). Several studies have shown an inverse relation between uric acid excretion and insulin level (42, 43). Insulin has also been found to promote the tubular reabsorption of sodium (44). Cappuccio and colleagues (45) reported an association of hyperuricemia with increased renal tubular sodium reabsorption, thus providing a link with hyperuricemia, hypertension, and hyperinsulinemia.

Uric acid may also be an indicator for increased oxidative stress. Xanthine oxidase, a critical enzyme in the degradation of purines to uric acid, has been shown to be an important source of superoxide free radicals (46). The activity of xanthine oxidase increases during ischemia and intensifies during reperfusion in coronary endothelial cells (47). In animals, allopurinol limits infarction size (48) and enhances recovery of stunned myocardium (49), perhaps by limiting the generation of toxic free radicals. Clinically, hyperuricemia occurs during interruption of limb arterial flow (50), after coronary angioplasty (51), during coronary artery bypass surgery (52), and in other hypoxic states (19, 20, 47, 53–56).

Several potential limitations of the present study should be considered. First, most participants were white. The results may not apply to nonwhite, non-

European populations. Second, data on several important clinical characteristics were unavailable. Renal function and insulin resistance were not measured at the time of data collection. Finally, the analyses in the diuretic and antihypertensive subgroups were limited by the number of participants in each category. The results of these subgroup analyses should be viewed as hypothesis-generating only.

Despite these limitations, however, we believe that our study adds to the current literature. This report is more contemporary than a previous Framingham Heart Study article (2) and included far more outcome events and subgroup analyses. Furthermore, the 23 years of follow-up in the current investigation is the longest to date. As a result, the number of outcome events is greater than in previously reported observational studies. We also adjusted for several relevant risk factors and potential confounders not available in many other cohort studies. Finally, each outcome event in this investigation was determined by a panel of three physicians according to a standardized protocol; other studies, in contrast, relied on death certificate or hospital record coding.

Our findings from a community-based prospective study of 6763 adult men and women suggest that an elevated serum uric acid level is not causally associated with increased risk for coronary heart disease, death from cardiovascular disease, or death from all causes. Associations reported in age-adjusted models are probably due to confounding, particularly by diuretic use. From a clinical perspective, serum uric acid level should not be used as an indicator of risk for cardiovascular disease; established risk factors should be used to stratify risk (57).

*Grant Support:* The Framingham Heart Study is supported by National Institutes of Health/National Heart, Lung, and Blood Institute contract N01-HC-38038. This investigation was supported in part by a research grant from Merck and Co., Inc. Dr. Culleton is a recipient of the 1997–1999 Kidney Foundation of Canada Fellowship.

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